REMARKS

Applicant has amended Claims 1, 3, 5, 13-16, 19-21 and 23, and canceled Claims 4 and 24. Thus, Claims 1-3, 5-11, 13-23, and 25 are presented for examination. The specific changes to the amended claims are shown above in the Amendments to the Claims, wherein the insertions are underlined and the ~~deletions are stricken through~~. Applicant responds below to rejections made by the Examiner in the Office Action of July 31, 2007.

I. Interview Summary

A telephonic interview was conducted on Tuesday, September 18, 2007. The participants in the interview were Examiners Larry Helms and Lynn Bristol on behalf of the Patent Office, and attorneys Mike Fuller and Erik Anderson on behalf of Applicant. During the interview, the participants discussed the enablement rejections to the pending claims and discussed claim limitations relating to adjusting pH conditions. No exhibit was shown. No final agreement was reached.

II. Election/Restrictions

Applicant elected Group I (Claims 1-25) in the Response to Restriction Requirement filed on May 23, 2006. Applicant has canceled the claims of Group II (Claims 26-29) without prejudice to their continued prosecution in one or more divisional, continuation, or continuation-in-part applications. Applicant respectfully submits that Claim 1 is generic to the species of Claims 8 and 9, all of which were included in Restriction Group I. Although Claims 8 and 9 recite species of endogenous antibody-cleaving enzymes that were not elected, Applicant respectfully submits that Claims 8 and 9 should be rejoined once the underlying base claim, Claim 1, is deemed allowable.

III. Rejections Withdrawn

Applicant acknowledges and thanks the Examiner for the withdrawal of the previous claim rejections based on § 112 as discussed in the present Office Action on pages 2-3.

III. Rejections Maintained Under 35 U.S.C. § 112

The Examiner has rejected Claim 19 (and dependent Claims 20, and 22-25) under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that in Claim 19, "it is unclear what is meant by 'activating.'" Applicant has

amended Claim 19 so that it now recites, *inter alia*, "activating endogenous aspartyl enzyme activity in said cell media by adjusting pH conditions of the cell media, such that said activating results in cleavage of said recombinant antibody into $F(ab')_2$ fragments.". The claims depending from Claim 19 thus also contain this limitation. Support for the amendment can be found in the present specification at, for example, paragraphs [0007], [0009], [0013], [0042]-[0044], [0050], and [0065], which discuss activating enzymes by adjusting pH. Applicant respectfully submits that the amendment clarifies the term "activating," and overcomes the rejection.

The Examiner has also rejected Claims 1-11 and 13-25 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Specifically, the Examiner states that:

> [T]he specification is not enabling for performing the method of *either* adjusting the temperature to just any degree or adjusting the pH to just any amount or in performing the steps in any order or manner, when instead the specification discloses a precise, step-wise order in which the method is to be performed.
>
> (a) The specification is enabling for a method of generating antibody fragments according to the method steps of clarifying the conditioned media, stabilizing the temperature at 37° C, and adjusting the pH to about 3.5 to activate endogenous enzymes for cleaving Ig molecules.

July 31, 2007 Office Action at 6. Claim 1 has been amended so that it now recites, *inter alia*, "adjusting pH conditions of the cell media to activate at least one endogenous enzyme in said cell media that cleaves said antibodies." Claim 19 has been amended so that it now recites, *inter alia*, "activating endogenous aspartyl enzyme activity in said cell media by adjusting pH conditions of the cell media, such that said activating results in cleavage of said recombinant antibody into $F(ab')_2$ fragments." The claims depending from Claims 1 and 19 thus also contain these limitations respectively. Support for these amendments can be found in the present specification at, for example, paragraphs [0007], [0009], [0013], [0042]-[0044], [0050], and [0065], which discuss activating enzymes by adjusting pH.

Applicant notes that the present specification discloses techniques for generating antibody fragments in addition to those that include "adjusting the pH to about 3.5." For example, experiments were also conducted with pH levels adjusted to 5.0, 4.5, 4.0, 3.5, 3.0, and 2.5. *See* Specification at page 15, paragraph [0050]. The notation in paragraph [0051] that "maximal" activity occurred at pH 3.5 should not be read to mean that 3.5 is the only pH that can be used. In

another experiment disclosed in the present specification, simultaneous activation of an aspartyl enzyme and deactivation of a cysteinyl enzyme was achieved by adjusting pH to 8.5. *See* Specification at page 13, paragraph [0043].

One having ordinary skill in the art will, upon reading the present specification, appreciate that not all enzymes are the same, and that reasonable experimentation will allow such a person to determine the optimal pH conditions for such different enzymes, and thus use the present invention within the scope of the claims. As discussed above, the specification provides working examples that encompass various digestion enzymes and multiple pH levels which are available to guide the practitioner having ordinary skill to carry out such a process by 1) using a cell line to raise antibodies, 2) cleaving the antibodies into fragments by activating an endogenous enzyme in the cell media by adjusting pH, 3) determining whether the resultant fragments have the sought after properties (such as antigen-binding capability), and then 4) isolating and purifying the fragments. Applicant respectfully submits that the amendments to these claims overcome the rejections.

The Examiner has also rejected Claims 1-11 and 13-18 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention.

More specifically, the Examiner alleges that Claims 1-11 and 13-18 are indefinite for the recitation of "said conditions" in line 8 of Claim 1 because Claim 1 includes "adjusted conditions," "pH conditions," and "temperature conditions," and it is unclear which conditions are being referred to as "said conditions." As amended, Claim 1 no longer recites "said conditions," but instead recites "said adjusted pH conditions." The claims depending from Claim 1 thus also contain this limitation. Support for the amendment can be found in the present specification at, for example, paragraphs [0007], [0009], [0013], [0042]-[0044], [0050], and [0065], which discuss activating enzymes by adjusting pH. Applicant respectfully submits that the amendment clarifies which "conditions" are referenced, and overcomes the rejection.

The Examiner has also rejected Claim 3, alleging that it is indefinite for lack of antecedent basis with regard to "the temperature." As amended, Claim 3 no longer recites "the temperature," and instead recites "temperature conditions." Applicant respectfully submits that the amendment overcomes the rejection.

The Examiner has also rejected Claims 4, 5, 16, and 17, alleging that these claims are indefinite for lack of antecedent basis with regard to "the pH" in Claims 4 and 5 and "pH" in Claims 16 and 17 (instead of "pH conditions"). Claim 4 has been canceled, and Claim 5 has been amended so that it no longer recites "the pH," and instead recites "a pH." With regard to Claims 16 and 17, the additional pH adjustment is related to a step for inactivating an enzyme rather than activating it (in contrast to the adjustment recited in Claim 1). Thus, Claim 16 has been amended to recite "adjusting a pH of the cell media." Claim 17, which depends from Claim 16, thus also includes this limitation. Support for the amendment to Claim 16 can be found, for example, in paragraph [0065], which discusses the irreversible inactivation of the cysteinyl enzyme by adjusting pH to 8.5. Applicant respectfully submits that the amendments overcome the rejections.

The Examiner has also rejected Claims 13-15 as allegedly being indefinite as being drawn to a "protein-free medium," "a peptone source," and "a CD-CHO media," respectively. The Examiner argues that Claim 1, from which these claims depend, requires a "protein-containing media" (because the cell media recited in Claim 1 contains at least one endogenous enzyme). The Examiner also alleges that a CD-CHO media would not likely contain proteins or peptides, and that a "peptone source" would unlikely contain whole enzymes. Thus, the Examiner alleges that "it is not understood how the method invention can be practiced in the absence of endogenous enzymes in the cell media."

As an initial matter, Applicant wishes to clarify the meaning of the phrase "at least one endogenous enzyme in said cell media" in Claim 1. The Examiner is correct that Claim 1 requires at least one endogenous enzyme in the cell media. However, in some embodiments, such an enzyme is made and secreted by the cells of the cell line, meaning that the starting media (such as, for example, a commercially available media like CD-CHO, mentioned in the specification at paragraph [0048]) need not contain proteins when the cell line is introduced. In this regard, the cell line can thus be the source of the endogenous enzyme(s) as well as the source of the antibodies to be cleaved by the endogenous enzyme(s). Applicant has thus amended Claims 13-15 to clarify this point, so that these claims no longer refer to "cell media," and instead refer only to "media," as in "a protein free media" in Claim 13, "a media comprising a peptone source" in Claim 14, and "a CD-CHO media" in Claim 15. Applicant has also amended

Claim 20 in a manner similar to that of Claim 15, to provide similar clarification. As amended, these claims refer to "media," which is intended to mean the nutrient environment that supports the cell line, and not necessarily the final cell media in which one or more enzymes is activated to cleave antibodies into antigen-binding fragments. With this distinction, Applicant submits that one having ordinary skill in the art can readily appreciate that a cell line can be grown (and thus be "provided") in a variety of media (including protein free media, for example, which may also be optionally supplemented with additional nutrients), and that the cell line can still produce protein products such as antibodies and digestive enzymes that end up in the "cell media" recited in Claim 1.

Applicant respectfully submits that the present specification provides sufficient teaching to support the amendments and clarifications with regard to this issue. For example, protein free media and peptone sources are discussed in paragraph [0058] of the present specification with reference to FIG. 1:

> The level of enzymatic activity in clarified, concentrated and activated cell culture medium that involved different fermentation conditions was examined. Enzymatic activity in fermentation conditions involving commercial media fortified with peptone sources or protein free media without peptone sources was examined using the N-check protease assay method. Fermentation conditions including protein free media without peptone sources showed a higher enzymatic activity than fermentation conditions including commercial media that was fortified with peptone sources (FIG. 1).

Specification at ¶ [0058]. Further, the use of CD-CHO medium is discussed in paragraph [0048] of the present specification:

> For the production of the antibody, cells were grown in stirred tank bioreactors using CD-CHO medium (Gibco-Invitrogen) supplemented with glucose, glutamine, pluronic F68, IGF-1 and proteose peptone No 3 (Becton Dikinson). Cell culture supernatant was harvested by filtration or centrifugation and passed through a sterile filter to remove particulate matter and cells prior to being subjected to the pH treatments and activation of enzymatic cleavage.

Specification at ¶ [0048]. Applicant thus respectfully submits that the use of a "protein free media" or a "CD-CHO media" to support a cell line does not require a conclusion that no enzymes or antibodies can be synthesized and/or secreted by that cell line. With regard to Claim

14, Applicant notes that the recitation that "the cell line is provided in a media comprising a peptone source" does not bear at all on whether whole enzymes are, or can be present. The open-ended transition "comprising" thus permits the presence of unrecited elements. Applicant respectfully submits that these amendments and clarifications overcome the rejections.

Accordingly, Applicant respectfully requests withdrawal of the § 112 rejections.

CONCLUSION

Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art.

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested. If the Examiner has any questions which may be answered by telephone, the Examiner is invited to call the undersigned directly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 10/19/2007

By: _____

Erik T. Anderson
Registration No. 52, 559
Attorney of Record
Customer No. 20, 995
(619) 235-8550

4310059
092507